

Remarks

In view of the following remarks, reconsideration of the outstanding office action is respectfully requested.

Filed herewith is a 37 CFR §1.132 Declaration of David Kaplan, Ph.D., an expert in the field of Natural Biomaterials. Also filed herewith are Zou, B., et al., *J. Mater. Sci.*, 41: 3357-3361 (2006) (Exhibit A) and Xie, F., et al., *Internat. J. Biolog. Macromol.*, 38: 284-288 (2006) (Exhibit B).

The U.S. Patent and Trademark Office ("PTO") has rejected pending claims 1, 2, and 4-31 under 35 USC § 112 (1st para) as failing to comply with the written description requirement. The PTO suggests that the specification does not support "that retain their native protein structure and have not been dissolved and reconstituted" in claim 1. Applicants respectfully disagree and wish to point out the support for the limitation found in paragraphs [0021] and [0022] of the specification, as follows:

[0021] ... "In a preferred embodiment, the sericin-extracted silkworm fibroin fibers **retain their native protein structure and have not been dissolved and reconstituted.**"

[0021] ... "'Natural' silk fibroin fibers are produced by an insect, such as a silkworm or a spider and **possess their native, as formed, protein structure.** Preferably, the silk fibroin fiber constructs are non-recombinant (i.e., not genetically engineered) and **have not been dissolved and reconstituted.**"

Therefore, the rejection as failing to comply with the written description requirement is improper and should be withdrawn.

The PTO has rejected all pending claims (claims 1, 2, and 4-31) under 35 U.S.C. §103(a) as being unpatentable over Li et al. (6,303,136) in view of O'Brien (7,014,807) and Lewis et al. (5,994,099) and Takezawa et al. (5,736,399).

Applicants respectfully disagree and request that this rejection be withdrawn for the following reason. Applicants submit that neither the patents and references cited in the outstanding office action, nor any other evidence of record, establish a *prima facie* case of obviousness.

Filed herewith is a 37 CFR §1.132 Declaration of David Kaplan, Ph.D., an expert in the field of Natural Biomaterials. The facts set forth in Professor Kaplan's declaration establish the following:

1. The combination or modification of the prior art references in the manner suggested by the PTO was contrary to the accepted wisdom in the art at the time of Applicant's invention. See Declaration of David Kaplan, Ph.D., at paragraph 17.
2. The combination or modification of the references in the manner suggested by the PTO would render the references inoperable for their intended purposes. See Declaration of David Kaplan, Ph.D., at paragraphs 6, 16, and 17.
3. One of ordinary skill in the art would not have had a reasonable expectation of success in combining the references suggested by the PTO. See Declaration of David Kaplan, Ph.D., at paragraphs 8, 15, and 17.

Claim 1 recites a fabric comprising a yarn comprising one or more sericin-extracted **fibroin fibers that retain their native protein structure and have not been dissolved and reconstituted**, said fibers being biocompatible and non-randomly organized, wherein said yarn promotes ingrowth of cells around said fibroin fibers and is biodegradable.

The PTO takes the position that *not* dissolving the silk fibroin fibers as disclosed by O'Brien would have been obvious when dissolving is not desired. Applicants respectfully disagree that O'Brien provides an option to dissolve or not to dissolve. As stated in the Declaration of David Kaplan, Ph.D., at paragraph 7:

"O'Brien discloses the production of regenerated polypeptide fiber. O'Brien teaches regeneration of decrystallized polypeptide by dissolving the silk protein, reconstituting it in solution, and re-spinning it to produce fiber threadline (O'Brien, Col. 3, line 50-64). O'Brien requires dissolving and reconstituting the native silk proteins and requires "decrystallized" silk flake to practice the teaching. See O'Brien, Col. 3, Line 50-57 and Claim 1. O'Brien does not provide an option to dissolve or not to dissolve the silk fibroin but requires dissolving."

Per the following quote from O'Brien (O'Brien, Col. 1, Lines 13-24), O'Brien is directed only to the production of synthetic fiber and teaches that mechanical properties are strongly dependent on chain length and orientation to the fiber axis.

The following is a quote from O'Brien (O'Brien, Col. 1, Lines 13-24):

"It is well known that the mechanical properties of **synthetic** organic fibers are strongly dependent upon the chain length of the molecules comprising them and their degree of orientation with respect to the fiber axis. If the molecular chain length falls below a certain level (which varies according to the type of material), the resulting chain ends and small molecules act as defects that substantially limit fiber tensile strength. It is therefore preferred in **synthetic fiber production** to extrude fibers from solutions or melts in which the number of low molecular weight molecules has been reduced as much as possible and that have the highest average chain length consistent with processibility." [emphasis added]

Therefore, O'Brien recognizes that longer, unbroken chains are desirable but chains higher than a certain length would not be compatible with the production process taught. See Declaration of David Kaplan, Ph.D., at paragraph 11. Consequently, O'Brien's requirement of using dissolved and reconstituted fibers teaches away from using undissolved fibroin fibers. See Declaration of David Kaplan, Ph.D., at paragraph 11.

As stated in the Declaration of David Kaplan, Ph.D., at paragraph 8:

"Accordingly, there was no reason apparent to one skilled in the art to make the suggested combination. In fact, without further processing, the regenerated polypeptide fiber of O'Brien would be

degradable and therefore, O'Brien teaches away from the combination of the references. In my opinion, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the references."

Dr. Kaplan further states in paragraphs 10 and 11 of his declaration that:

"The fibers produced by the decrystallization and reconstitution process of O'Brien differ significantly from the fibers of the present invention in their physical and mechanical properties. The fibers produced from the reconstituted protein are composed of sections of polymer of variable length. See O'Brien, Col. 1, Lines 13-24. The polymer sections overlap to various extents and may or may not be oriented parallel to the axis of the fiber. Also, the numerous chain ends of the polymer sections act as defects that substantially limit fiber tensile strength. Conversely, the fibers of the present invention are essentially unbroken polymer chains without the attendant deficiencies described above."

"O'Brien teaches that if the chain lengths are too short the chain ends act as defects resulting in brittle fibers. And that it is preferred to have the highest average chain length possible. (O'Brien, Col. 1, Lines 16-24) With this in mind, O'Brien still requires dissolving and reconstituting the native silk proteins and requires "decrystallized" silk flake to practice the teaching. (O'Brien, Col. 3, Line 50-57 and Claim 1) The difference between fibers that are each made up of an essentially unbroken polymer as in the present invention and the properties inherent in such a fiber must be contrasted with fibers produced from decrystallized polymer. The properties of dissolved and reconstituted fibers (also known as regenerated silk fibroin) have been shown to differ significantly from native silk fibroin (which have not been dissolved and reconstituted). See Zou, B., et al., *J. Mater. Sci.*, 41: 3357-3361 (2006) and Xie, F., et al., *Internat. J. Biolog. Macromol.*, 38: 284-288 (2006), attached as Exhibits A and B. The decrystallized/reconstituted protein results in short sections of polymer of various orientations and the attendant disruption and change of mechanical properties. Native and decrystallized polymers are no more comparable than a piece of wood (native) is to a piece of paper (reconstituted)."

Dr. Kaplan further concludes that “It is my expert opinion that O’Brien provides no suggestion or motivation to use sericin-extracted fibroin fibers that retain their native protein structure and have not been dissolved and reconstituted as required by the present claims.” See Declaration of David Kaplan, Ph.D., paragraph 12.

Li teaches an encapsulation device having a non-degradable filamentous matrix surrounded by a semi-permeable membrane (Li, Col. 3, lines 48-55)(Declaration of David Kaplan, Ph.D., paragraph 6). The encapsulation device is designed to contain cells or tissue for implantation within a host that in the absence of the membrane would provoke an immune response from the host (Li, Col. 6, lines 34-36)(Declaration of David Kaplan, Ph.D., paragraph 6).

In Dr. Kaplan’s expert opinion, “Li teaches away from the present invention by teaching the matrix be made from “substantially non-degradable” fibers (Li, Col. 3, line 1). Li teaches that degradation would render the invention inoperable: “A “biocompatible capsule” is a capsule that, upon implantation in a host mammal, does not elicit a detrimental host response sufficient to result in the rejection of the capsule or to render it inoperable, such as through degradation.” (Li, Col. 6, lines 43-46, emphasis added).” See Declaration of David Kaplan, Ph.D., paragraph 6.

Lewis teaches cloned DNA encoding spider flagelliform silk protein (Declaration of David Kaplan, Ph.D., paragraph 13). As in O’Brien, Lewis teaches formation of fibers from **dissolved** protein (Lewis, Col. 20, line 37)(Declaration of David Kaplan, Ph.D., paragraph 13).

Takezawa teaches a culture-carrier of natural or synthetic threads (Declaration of David Kaplan, Ph.D., paragraph 16). According to Dr. Kaplan, “[t]he use of the degradable, dissolved and reconstituted silk fibers of O’Brien or Lewis would render the device of Takezawa inoperable. The use of degradable fibers would not achieve the

intended advantage of “providing a novel culture carrier in which animal cells can proliferate three-dimensionally.” See Declaration of David Kaplan, Ph.D., paragraph 16.

While applicants respectfully disagree that the cited references are combinable, assuming, *arguendo*, one was to combine the references, the combination would not result in the claimed invention. See Declaration of David Kaplan, Ph.D., at paragraph 17. The combination would result in the device of Li or the device of Takezawa made from the degradable synthetic fibers of O’Brien or Lewis. The use of degradable fibers would render the devices inoperable. See Declaration of David Kaplan, Ph.D., at paragraph 17.

In light of the above, the PTO’s burden of establishing a *prima facie* case for an obviousness rejection has not been met, therefore the rejection under 35 U.S.C. §103(a) is improper and should be withdrawn.

The PTO has rejected all pending claims (claims 1, 2, and 4-31) on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,902,932 B2 in view of O’Brien. The rejection is respectfully traversed in view of the arguments above against reliance on O’Brien.

As stated in the Declaration of David Kaplan, Ph.D., at paragraph 7, “O’Brien teaches regeneration of decrystallized polypeptide by dissolving the silk protein, reconstituting it in solution, and re-spinning it to produce fiber threadline (O’Brien, Col. 3, line 50-64).” Thus, the combination of U.S. Patent No. 6,902,932 B2 and O’Brien would not teach or suggest the claimed invention.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

The PTO is authorized to charge and fee deficiencies or credit any overpayments associated with this submission to the Nixon Peabody LLP Deposit Account No. 50-0850.

Customer No. 50828

Respectfully submitted,

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